Received: 2 January 2017 | Accepted: 9 August 2018

DOI: 10.1002/osi2.1001

REVIEW ARTICLE

WILEY Oral Science International
Official Journal of the Japanese Stomatological Society

Titanium exposure and human health

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Abstract

Historically, titanium (Ti) has maintained the reputation of being an inert and relatively biocompatible metal, suitable for use in both medical and dental prosthesis. There are many published articles supporting these views, but there is recent scientific evidence that Ti, or its corrosive by-products, may cause harmful reactions in humans. It is important for all medical and dental professionals to understand the implications, complexities, and all potential pathways of exposure to this metal. These exposures are not only from the environment but also through various commonly used products in medicine that are often completely overlooked. These external (intermittent) and internal (constant) exposures have an impact on whole-body health. This review examines possible harmful effects, risks, and often ignored potential complications of Ti exposure to human health.

KEYWORDS

electromagnetic frequency, nanoparticles, titanium dental implants

1 | INTRODUCTION

Titanium is widely distributed and constitutes 0.44% of the earth's crust. The metal is found combined in practically all rocks, sand, clay, and other soils. It is also present in plants, animals, natural waters, deep-sea dredgings, meteorites, and stars. Ti's atomic number is 22.[1] Ultrafine Ti dioxide (TiO_2) is commonly used in a number of applications, including food additives, food packaging material, sunscreens, cosmetic creams, and as a component of surgical implants. There are rising concerns over exposure to TiO_2 nanoparticles (NPs) during critical windows, such as pregnancy and lactation, for women and men of reproductive age, and last but not least, childhood exposure to high cumulative doses.[2] We have included in our discussion various source points of Ti and how its use with other metals may lead to increased health risks due to galvanic corrosion.

2 | TITANIUM DIOXIDE NANOPARTICLES (TIO_2 NPS)

The cytotoxic effect of Ti particles is size dependent, since they must be smaller than that of cells.[3] TiO_2 exists naturally, mainly in the form of three crystalline structures: rutile, anatasa, and brookite. In Ti implants, the passivant oxide layer is made up of anatasa and rutile or anatasa alone.[4] Ti in dentistry is widely used as an implant in the form of membranes, grids, reduction plates, screws, and distractors, among other applications. In 2009, about 300 000 patients in the United States received dental implants. Since no metal or alloy is entirely inert, in vivo corrosion can occur.[4] Khan et al[5] compared the cytotoxic and genotoxic potential of zinc oxide NPs (ZnO) and TiO_2 NPs using various concentrations. Both NPs were found to create reactive oxygen species (ROS) concomitant with the depletion of glutathione (GSH) and glutathione S-transferase (GST) levels and increased superoxide dismutase (SOD), chloramphenicol acetyl transferase (CAT), and lipid peroxidation in a dose-dependent manner. Both NPs exerted roughly equal oxidative stress in terms of the above stress markers. This study affirmed that ROS generation is the main mechanism to cause various types of toxicities by ZnO and TiO_2 NPs. These results clearly suggest that both ZnO and TiO_2 NPs are significantly cytotoxic, and also genotoxic at all concentrations with respect to untreated samples or controls. While comparing with ionic forms, no significant difference was found.[5] Ghosh et al[6] evaluated the toxic effects of commercial TiO_2 NPs by using a series of

cytotoxic, genotoxic, hemolytic, and morphological parameters. Their results suggest that the TiO_2 NPs could induce significant reduction in mitochondrial dehydrogenase activity in human lymphocyte cells. This study showed that TiO_2 NPs provoked DNA damage and cell death in a dose-dependent manner. Dobrzyńska et al[7] aimed to investigate the cytotoxicity and genotoxicity of TiO_2 and silver (Ag) NPs at different doses and particle sizes to bone marrow cells. Negative responses were shown in reticulocytes (micronuclei) and in leukocytes (Comet assay) of bone marrow. Results indicated that different bone marrow cells display different susceptibilities toward genotoxicity mediated by both investigated NPs. The use of materials containing NPs and the potential health implications of exposure to them should be monitored.[7] The presence of metallic particles in peri-implant tissues may not only be due to a process of electrochemical corrosion but also to frictional wear, or a synergistic combination of the two.[8] Additionally, mechanical disruption during insertion, abutment connection, or removal of failing implants has been suggested as a possible cause of the release of particles from metal structures. The release of particles/ions from the implant into the surrounding biological compartment, their biodistribution in the body, and their final destination are issues that lie at the center of studies on biocompatibility and biokinetics.[8] Clinical studies have already demonstrated that TiO_2 NPs together with metallic ions released from implants accumulate in peri-implant tissues. Particles size range from nanometer to micrometer scale.[9] Therefore, if the removal of an existing Ti implant is being considered, extreme care should be taken so that the patient (in particular pregnant women) and dental personnel are protected from the potential inhalation of Ti particles. In recent years, nanomaterials have been widely used in the production of dental materials. However, the dental applications of nanomaterials yield growing concerns regarding their safety. Disdier et al[10] recently reported their findings on time-related responses from single-dose intravenous (IV) administration of 1 mg/kg TiO_2 NPs to rats, with particular emphasis on Ti quantification in the brain. Ti content in tissues was analyzed using inductively coupled plasma mass spectrometry. Integrity and functionality of the blood-brain barrier (BBB), as well as brain inflammation were characterized using a panel of methods including RT-PCR, immunohisto chemistry, and transporter activity evaluation. Their results showed Ti biopersistence in the liver, lungs, and spleen up to 1 year after TiO_2 NPs administration. A significant increase of Ti in the brain was observed at early end points followed by a subsequent decrease. Exposure of an in vitro BBB model to sera from TiO_2 NPs-treated animals confirmed the tightness of the BBB and inflammatory responses. While some studies have shown that NPs can cross the placenta barrier in pregnant mice and cause neurotoxicity in their offspring, Yamashita et al[11] showed that silica and TiO_2 NPs with diameters of 70 and 35 nm, respectively, can cause pregnancy complications when injected intravenously into pregnant mice. The silica and TiO_2 NPs were found in the placenta, fetal liver, and fetal brain. Mice treated with these NPs had smaller uteri and smaller fetuses than untreated controls. Mohammadipour et al[12] found that exposure to TiO_2 NPs during pregnancy on Wistar rats significantly reduced cell proliferation in the hippocampal and significantly impaired the learning and memory in the offspring. Observations made with a transmission electron microscope demonstrated the incorporation of TiO_2 NPs into vacuoles of the cells. TiO_2 NPs significantly enhanced the Interleukin-1 beta (IL-1β)-induced prostaglandin Estradiol (E2) production, which, induces uterus contractions and cyclooxygenase (COX-1 and 2) protein expression. IL-1β reduced the intracellular concentrations of overall primary metabolites, especially those of amino acid, urea cycle, polyamine, S-adenosylmethione, and GHS synthetic pathways.[13] The addition of TiO_2 NPs further augmented these IL-1β-induced metabolic changes, recommending careful use of dental materials containing TiO_2 NPs with regard to patients with gingivitis or periodontitis.[13] Tissue distribution and blood kinetics of various TiO_2 NPs were investigated in rats up to 90 days postexposure after oral and IV administration of a single or five repeated doses. Single and repeated IV exposure of Ti resulted in rapid distribution from the systemic circulation to all tissues evaluated. The main target tissue was the liver, followed by the spleen, and lung. The present oral and IV study concluded that very low oral bioavailability, along with slow elimination might result in potential tissue accumulation.[14] Xu et al[15] found that exposure to TiO_2 NPs increased *Staphylococcus aureus* infection of HeLa cells. In their experiment when HeLa cells were pretreated with TiO_2 followed by exposure to *S. aureus* bacteria, their data showed that the number of bacteria associated with the HeLa cell membrane increased. Also, a substantial increase in the number of bacteria per cell indicated that the cell membrane became more permeable to the bacteria. Their results indicate that exposure of tissue to TiO_2 NPs may significantly increase the risk of bacterial infection.[15] Subacute and chronic changes from TiO_2 NPs exposure were reported to induce pulmonary response in rabbits. There were limitations in that the sequential acute changes following TiO_2 exposure were not investigated.[16] Choi et al[16] used image analysis in their study to evaluate acute lung inflammation following TiO_2 NPs intratracheal instillation. They observed ground glass opacities of acute pneumonitis at 1 hour after single P25 TiO_2 NPs exposure. Also observed was persistent pneumonitis in the P25 TiO_2-exposed lung, as well as newly developed pneumonitis in the P25 TiO_2-unexposed opposite lung at 24 hours. These results indicate that a single instillation of P25 TiO_2 can induce severe acute pulmonary inflammation. Additionally, previous studies reported that high-dose TiO_2 NPs cause more severe lung inflammation compared with that of low-dose TiO_2, as well as inducing persistent pulmonary inflammation. This information may have clinical implications regarding safety in handling of TiO_2 NPs.[16] Husain et al[17] showed that a small fraction of TiO_2 NPs translocate from the lungs to blood and extrapulmonary organs, using a nano-hyperspectral microscope. Adult female mice C57BL/6 exposed via intratracheal instillation to 18 or 162 μg of industrially relevant TiO_2 NPs alongside vehicle controls showed translocation to the heart and liver at both doses, and the blood at the highest dose, in mice analyzed 24 hours postexposure. Acute translocation of particles to blood and other organs coincides with the induction of an innate immune type response, which includes the activation of acute stress in liver. Adding to this, C3

activation in blood was found, and the activation of complement cascade and inflammation response in the heart tissue, all of these processes are involved in particle recognition and clearance.[17] IV injection of TiO_2 NPs at high doses in mice caused acute toxic effects in major target organs.[18] Ti accumulates in many organs mainly liver, kidneys, spleen, lungs, brain, and heart. Nano-anatase TiO_2 at a higher dose caused serious damage to the liver, kidney, and myocardium of mice and disturbed the balance and metabolism of blood sugar and lipid in mice.[19] Mice subacutely exposed to 2-5 nm TiO_2 NPs showed a significant, but moderate inflammatory response among animals exposure after 1 or 2 weeks, which resolved by week 3 postexposure.[20] Using naïve mice and mice with ovalbumin (OVA)-induced airway inflammation showed that the inhalation of TiO_2 might aggravate respiratory diseases, and the adverse health effects are highly dependent on dose and timing of exposure. Data imply that inhalation of NPs may increase the risk for individuals with allergic airway disease of developing symptoms of severe asthma.[21]

3 | EFFECTS OF ELECTROMAGNETIC RADIATION ON TI IMPLANTS

Crouzier et al[22] investigated magnetic resonance imaging (MRI), electromagnetic frequency/field (EMF), radiofrequency radiation (RFR), and its relationship with implantable devices. It has been discovered that a significant part of the population bears metallic devices including orthopedic plates, rods, screws, prosthesis but also dental implants, stents, electrodes wires, or electronic devices. Metallic devices are well known to strongly interact with EMF by diffraction or focusing thus, leading to a significant local enhancement of field intensity.[22] With the use of electronic devices, such as cellphones or personal computers (PCs), becoming increasingly prevalent in recent years, many articles only emphasize the convenience of these electronic devices without addressing the potentially negative influences of the emitted electromagnetic waves on the body.[23] Metals present within the body can act as an antenna to collect harmful radio waves, thus inducing many general and severe symptoms, such as headaches, fatigue, tinnitus, dizziness, memory loss, irregular heartbeats, and whole-body skin symptoms, which are considered to be caused by electromagnetic hypersensitivity. In dentistry, Ti dental implants may be the material most commonly associated with antenna activity and may promote harmful effects of electromagnetic waves. Dental treatments should be performed in a manner that avoids the harmful influences of radio waves on patients.[23] We believe this can be accomplished by using biocompatible nonmetal dental materials. Metallic implants amplify high frequency (HF)-EMF 100-700 folds nearby and exceed the safety levels. If dental metals (crowns, fillings, bridges, Ti implants) are implanted in the upper jaw, HF-EMF is enhanced in the cranial nerves and brain. The presence of dental metals may increase the risk for HF-EMF-induced brain cancers several fold and should be acknowledged as confounding variable in future studies, exploring brain cancer risk in dependence of HF-EMF exposure.[24] Patients with severe or fatal illnesses (like amyotrophic lateral sclerosis (ALS), Alzheimer's, Parkinson's, cancer, multisystemic atrophy, multiple sclerosis (MS), severe elektrohypersensitivity, Multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), and severe chronic pain (neuralgia, migraine) often have pieces of dental metals, mostly mercury (Hg) amalgam, in the jaw bone.[24] Yakymenko et al[25] looked at 100 available peer-reviewed studies dealing with low-intensity RFR; 93 of these studies confirmed that RFR induces oxidative effects in biological systems. The oxidative efficiency of RFR can be mediated via changes in activities of key ROS. ROS and their involvement in cell signaling pathways explains a range of biological/health effects of low-intensity RFR, which include both cancer and noncancer pathologies. In turn, a broad biological potential of ROS and other free radicals, including both their mutagenic effects and their signaling regulation, makes RFR a potentially hazardous factor for human health. The modern data on the biological effects of low-intensity RFR leads to a firm conclusion that this physical agent is a powerful oxidative stressor for living cells.[25] The database used by Yakymenko[25] was about 18 months old, when that paper was published. As of July 8, 2015, there had been 153 papers published on the oxidative stress effect of RFR, of which 90% (137 papers) showed effect vs 10% (16 papers) reporting no effect. Thus, there is overwhelming peer-reviewed research confirming the potential harmful effect of radiofrequency radiation.[26] Sometimes head and neck cancer patients treated with high-energy X-rays and gamma rays have Ti dental implants. Ti dental implants in the field of irradiation were capable of causing significant radiation scatter. Therapists involved in radiation planning should consider dental implants on the radiation beam as a presumed cause of osteoradionecrosis.[27] The calculations showed that the presence of a dimension-reduced implant results in remarkable differences in the dose distribution all around the implant. Similar to standard implants, the risk for dose enhancement was notably important for the bone in direct contact with the implant.[28] For the different radiation beams studied, the irradiation angle between scattering Ti dental implants and the central axis does not significantly affect the total dose that may lead to osteoradionecrosis of the mandible.[29] Animal and human studies indicate that irradiated bone has a greater risk of implant failure than nonirradiated bone. This increase in risk may be up to 12 times greater.[30] Implant therapy is no longer considered impossible for patients who have received radiation treatment for head and neck cancer. However, the risk of osteoradionecrosis and failed osseointegration are barriers to implant therapy for this population.[31] There is a significant increase in the risk of implant failure in irradiated patients (risk ratio: 2.74; 95% confidence interval: 1.86, 4.05; $P < 0.00001$) and in maxillary sites (risk ratio: 5.96; 95% confidence interval: 2.71, 13.12; $P < 0.00001$). Conversely, hyperbaric oxygen (HBO) therapy did not reduce the risk of implant failure (risk ratio: 1.28; 95% confidence interval: 0.19, 8.82; $P = 0.80$). Radiotherapy was linked to higher implant failure in the maxilla, and HBO therapy did not improve implant survival.[32] There is a risk of radio frequency (RF) heat generation within Ti. 3.0 T-MRI scanners are becoming increasingly common. The specific absorption rate (SAR) of 3.0 T-MRI is quadruple that of SAR compared

with 1.5 T-MRI, due to its being proportional to the square of the strength of a static magnetic field. The effect of heat generation on 3.0 T-MRI can thus be greater than on 1.5 T-MRI. The rise in temperature of Ti implants was measured to be a maximum of 0.4°C.[33] The impact of magnetic force from an MRI on dental materials will attract iron-containing (or ferromagnetic) objects and may cause them to move suddenly and with a great force like a "missile". This can cause possible risks to patients or anyone in an objects "flight path". It can pull any ferromagnetic object in the body too. Tissue injury can be caused due to heating the prosthesis. RF heating was confirmed to take place at both ends of the implants in spite of their different shapes. It is recommended to treat all material as MR unsafe, if the dentist is not sure about the type of prosthesis/appliance. It is advisable to remove the prosthesis/appliances prior to MRI.[34]

4 | ROOT CANAL SEALERS USING TI

There are many contraindications for dental materials that are commonly used, however, in-depth health histories are often not examined prior to dental treatments, nor are there follow-up visits with patients for any potential negative reactions from these materials. For example, even after a complete root canal therapy, reinfection may occur as a result of incomplete seal and activation of residual bacteria. Thus, antimicrobial activity is an important characteristic of root canal sealers. These two filling materials, MTA Fillapex and AH 26, were exposed to the bacterial suspension of Enterococcus faecalis, Escherichia coli, Streptococcus mutans, and Candida albicans after setting. Regarding all four bacterial groups, the bacterial count was significantly lower in the MTA Fillapex group when compared to the AH 26 group.[35] AH 26 showed in vitro estrogenic effect, but not AH Plus. AH 26-powder induced MCF-7 cell proliferation in a dose-dependent manner. The endodontist must consider the possible estrogenic effect of AH 26, as well as the cytotoxic effects of root filling materials, and avoid the leakage of sealer through the apex during root canal treatment.[36] DENSTPLY AH 26 Root Canal Sealing and Filling Materials are composed of the following: (AH 26, powder): Bismuth oxide, Methenamine, Silver, TiO_2; (AH 26 silver free, powder): Bismuth oxide, Methenamine, and AH 26 resin: Epoxy resin.[37] The contraindications, warnings, and precautions are as follows: hypersensitivity against epoxy resins or "other components" of the root canal filling material. AH 26 and AH 26 silver free contain epoxy resins, which may cause sensitization in susceptible persons. During the setting reaction of both materials, traces of formaldehyde are produced.[37] Do not use AH 26 and AH 26 silver free in persons allergic to epoxy resins. We recommend that these contraindications be discussed with patients prior to treatment, and as mentioned earlier, biocompatibility testing be preformed on all potential materials that may be used. Avoid contact of powder or resin and unset paste with skin or oral mucosa. After incidental contact, wash and rinse with plenty of water. Wear protective gloves and glasses. Interaction with other dental materials: AH 26 and AH 26 silver free may react with hydrogen peroxide accidentally left in the root canal after irrigation. Adverse Reactions: With sealers containing epoxy resins, the following adverse reactions were reported, including reversible acute inflammation of the oral mucosa after contact with the unset paste. In individual cases, local and systemic allergic reactions have been reported.[37] MTA Fillapex composition is as follows, salicylate resin, bismuth trioxide, fumed silica, TiO_2, mineral trioxide, aggregate (40%), and base resin. MTA Fillapex is a root canal sealer intended for the permanent sealing of root canals and may be used in combination with root canal obturation materials. Contraindications and warnings are as follows: In patients with hypersensitivity against the resins or other components of the product.[38] MTA Fillapex contains resins, which may sensitize susceptible individuals. Do not use it in patients allergic to the resins or "other components" of the product; avoid contact with eyes or skin. In case of contact, rinse immediately with water; avoid contact with oral mucosa. In case of contact, rinse with water and prevent swallowing of product. In case any sensitivity persists, seek medical attention promptly; if the syringe becomes contaminated with saliva or blood during application, dispose of the syringe and do not use on an additional patient. Ensure that the lids of the base paste and catalyst are not switched, because switching them can cause hardening of the product inside the tube.[38] The cytotoxicity of three different types of root canal sealers on human periodontal ligament (PDL) cells and a permanent hamster cell line (V79 cells) were examined. The results showed that elutes from resin-based, zinc oxide-eugenol-based, and calcium hydroxide-based sealers were cytotoxic to primary human PDL cultures and V79 cells.[39] Calcium hydroxide-based sealer was the least toxic sealer among the chemicals tested in both cultures. The results confirmed that root canal sealers constantly dissolve when exposed to an aqueous environment for extended periods, possibly causing moderate or severe cytotoxic reactions.[39] GuttaFlow (Roeko) silicone-based sealer, AH plus (De Tray-DENTSPLY) epoxy resin-based, Apexit (Vivadent) calcium hydroxide-based, and Endorez (Ultradent) methacrylate-based sealers were tested on primary cell lines of human gingival fibroblasts. All four sealers showed different cytotoxicity effects on primary cell lines of human gingival fibroblasts, but all of them are slightly cytotoxic.[40] Reszka et al[41] evaluated the chemical elements in two new calcium silicate-containing root canal sealers, BioRoot RCS and Well-Root ST and compared them to MTA Fillapex and AHPlus sealer. Studies have assessed the chemical elements and heavy metals in MTA Fillapex and AHPlus, but the authors noted that the two novel calcium silicate-containing root canal sealers, to the best of their knowledge had not been analyzed. Using energy-dispersive spectroscopy (EDS) X-ray microanalysis and scanning electron microscopy (SEM), EDS showed that BioRoot RCS did not have heavy metals or other toxic elements, while microanalysis revealed that Well-Root ST contained aluminum and Ti in addition to calcium, zirconium, oxygen, carbon, and silicon. This study concluded that BioRoot RSC had the highest degree of purity. Further investigation of the heavy metals contained in Well-Root, MTA Fillapex, and AHPlus is warranted due to the clinical implications for the patients.[41]

5 | CORROSION OF TI

5.1 | Galvanic corrosion

Titanium implants used outside of the mouth have exhibited failure through a foreign body reaction. Phenomena occurring in the body, such as passive dissolution, osteolysis, and metallosis have not been discussed relative to dental implants. The dental community must consider the full spectrum of implant interactions within the body to understand the differences and similarities within the mouth.[42] Also, what is alleged to be commercially pure Ti has been shown to contain impurities of other metals, such as nickel (Ni), which may have clinical significance.[43] Studies have shown that Ti is released in the presence of biological fluids and tissues. There are some signs of Ti penetration through the oral mucosa. While the structure of skin and the oral mucosa are similar, the permeability of the floor of the mouth is up to 4000 times higher than the skin. Although there are some methods for testing reactivity to Ti, Ti allergy is mainly diagnosed through clinical evaluation.[43] The oral cavity is one of the most inhospitable environments in the human body and is subject to larger temperature and pH variations than most other parts of the body. Corrosion caused by the graded degradation of materials by electrochemical attack, is of concern, particularly when dental implants are placed in the hostile electrolytic environment provided by the human mouth. Allergic reactions may occur from the presence of ions produced from the corrosion of implants.[44] The issue of corrosion may not be limited to a local problem because particles produced as a result of corrosion may migrate to sites far from the implant. This subject is of particular interest in studies of biocompatibility.[4] The abnormal electrical currents produced during corrosion can convert any metallic implant into an electrode, and the negative impact on the surrounding tissue due to these extreme signals is an additional cause of potential poor performance and rejection of implants. Metal traces originating from dental implants have been found in blood, liver, lungs, and lymph nodes.[4,19,45] These metal ions and wear debris may also contribute to aseptic loosening by promoting inflammatory complications that may result in macrophage activation, bone reabsorption, and, rarely, in the potential development of neoplasia. Recently, TiO_2 was classified as possibly carcinogenic to human beings by the International Agency for Research on Cancer (IARC).[4,45] Corrosion can occur in any dental prosthesis, and it may be accelerated by the use of a high proportion of base metal.[46] Chaturvedi[44] found that Ti implants and their presence in the human body may also cause internal exposure, which ultimately leads to Ti ions to concentrate in tissues, regional lymph nodes, and pulmonary tissue. The potential toxicity and biological risks associated with ions and/or particles released, due to corrosion of metallic implants is a health concern for patients with prostheses (orthopedic and/or dental) due to the long duration that these implants stay inside the body.[44] Six basic factors are involved in galvanic corrosion: (a) potentials, (b) polarization, (c) electrode areas, (d) resistance and galvanic current, (e) the electrolyte medium, (f) aeration, diffusion and agitation of the electrolyte. Galvanic coupling is a galvanic cell in which the more negative metal (anode) is the less corrosion-resistant metal than the more positive metal (cathode).[47] The galvanic corrosion of dental devices is important in two respects: (a) the biological effects which may result from the dissolution of alloys and (b) the current flow resulting from galvanic cell that could cause bone destruction.[47] Ti was anodic to noble alloys and cathodic to iron (Fe)- and Ni-based passivizing alloys. It was shown that the galvanic corrosion resistance of mentioned alloys coupled with Ti from the highest to lowest are as follows: High Copper (Cu) dental amalgam > Low Cu dental amalgam > Gallium-based direct filling.[47]

5.2 | Common oral treatments

Toothpastes, mouthwashes, and prophylactic gels contain from 200 to 20 000 ppm fluoride and can impair the corrosion resistance of dental alloys in the oral cavity. Adding fluoride to the solution made the Ti's potential more active and enhanced the corrosion of Ti in combination with high-Cu amalgams. The combination of low pH and the presence of fluoride ions in solution severely affects the breakdown of the protective passivation layer that normally exists on nitinol and Ti alloys, leading to pitting corrosion.[47] Galvanic corrosion occurs more actively and many metal ions are released with a higher potential difference or poorer corrosion resistance. The release of metal ions into the oral cavity can be harmful to the cells of the adjacent tissues, and they may cause side effects including cytotoxicity, allergies, and mutagenesis. Cytotoxicity was significantly increased in all groups where Ni-Chromium (Cr) alloys were in contact with Ti.[46] Corrosion release of the several substitutional alloying elements from various Ti alloys used in dentistry have been widely known. It has been reported that these metal ion releases are associated with the carcinogenic and mutagenic activity of the oral cavity. Several studies have further shown that the cellular uptake of hexavalent Cr is many folds greater than the trivalent Cr ion and its increased uptake causes a reduction in the alkaline phosphatase activity of the osteoblastic cells.[48] Increasing evidence is found that Ti and various substitutional alloying elements leach into the crevicular space around the implant. The potential adverse effects of metal ion release into living tissues can be proposed based on information from literature and various clinical, preclinical, and animal trial studies in vivo and in vitro. It is clear that corrosion is bound to occur and its consequences can be quite severe.[48] The potential toxicity and biological risks associated with ions and/or particles released due to corrosion of metallic implants is a public health concern for any patient who has a prosthesis (orthopedic and/or dental), since these prostheses remain inside the body over long periods of time, sometimes a lifetime. Likewise, the subject of corrosion is of interest to researchers; corrosion studies aim at avoiding the possible corrosion-related health problems that may arise when metallic implants are placed in humans.[7]

6 | TI's HEALTH RISKS AND RELATED DISEASES

6.1 | Hypersensitivity

A systematic review by Javed et al[49] examined whether Ti sensitivity is associated with allergic reactions in patients with dental implants. Their investigation showed that impurities, while small were consistent in the Ti alloys such as sponge Ti, TiAl6V4, and iodide Ti. Also found were other elements such as beryllium (Be), cobalt (Co), Cr, Cu, (Fe), Ni, and palladium (Pd) and these elements may contribute to triggering an allergic response in patients with dental implants. Patch testing (PT) and lymphocyte transformation testing (LTT) was preformed on 16 patients with revised metal-on-metal arthroplasty and peri-implant lymphocytic inflammation. In 13/16 (81%) of the patients, systemic metal sensitivity was found based on the PT and/or LTT testing. Thomas et al[50] concluded that the lymphocyte dominated peri-implant inflammation might well reflect an allergic hyperreactivity in these patients, due to the high rate of concurrent metal allergy found among them. There is supporting literature that Ti can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this reactive metal. There are reports about the corrosion of dental implants and their significance when hypersensitivity is present.[51] Müller and Valentine-Thon[52] reported on 56 patients who had developed clinical symptoms after receiving Ti-based implants. The patients were tested in the optimized lymphocyte transformation test MELISA against 10 metals including Ti. Fifty-four patch-tested patients were negative to Ti. Following removal of the implants, all 54 patients showed remarkable clinical improvement. In the 15 retested patients, this clinical improvement correlated with normalization in MELISA reactivity. These data clearly demonstrate that Ti can induce clinically relevant hypersensitivity in a subgroup of patients chronically exposed via dental or endoprosthetic implants.[52] One of the most fundamental criteria is the interaction between the surrounding physiological environment and the surface of the implant itself. This interaction can lead to either the failure of the implant to function, as it was intended, or have an adverse effect on the patient. Metal sensitivity may arise after exposure to Ti for some patients in certain circumstances.[51] Sodor et al[53] examined a variety of orthodontic biomaterials to evaluate the biocompatibility like stainless steel arch wires, brackets, and Ni-Ti alloy coil springs. These studies were performed in vitro using human fibroblasts cells on which the orthodontic materials were applied. The positive control was the Cu amalgam. Readings of the cell reactions were performed at 3 and 6 days. They concluded that *all* biomaterials analyzed caused cellular changes of varying intensity without necessarily showing a cytotoxic effect.[53]

Hypersensitivity to biomaterials is often defined in terms of ambiguous pain, skin rashes, lethargy, and malaise and in some cases implant loss.[54] At present, little is known about Ti hypersensitivity, but it cannot be excluded as a reason for implant failure. Ti can induce hypersensitivity in susceptible patients and could play a critical role in implant failure.[54]

6.2 | Allergic reaction

Syed et al[55] showed that more reports were published in which dekeratinized hyperplastic reactions of the peri-implant tissues and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome suggestive of Ti allergy were observed in association with Ti implants. A patient demonstrating a DRESS syndrome, which reflects a serious hypersensitivity reaction to drugs, in association with Ti bioprosthetic implants was recently reported. Ti implants can corrode and release ions or micro-particles, which can induce inflammation in affected tissues.[51] Sicilia et al[56] evaluated 1500 patients with dental implants. Thirty-five subjects out of 1500 implant patients treated and/or examined (2002-2004) were selected for Ti allergy analysis. Sixteen presented allergic symptoms after implant placement or unexplained implant failures in the allergy compatible response group (ACRG), while 19 had a history of other allergies, or were heavily Ti exposed during implant surgeries or had explained implant failures (predisposing factors group [PFG]). Thirty-five controls were randomly selected (CG) in the Allergy Centre. Cutaneous and epicutaneous tests were carried out. Nine of the 1500 patients displayed positive reactions to Ti allergy tests (0.6%): eight in the ACRG (50%), one in the PFG (5.3%) (P 1⁄4 0.009), and zero in the control group. Five positives were unexplained implant failures (five of eight). Harloff et al[57] used spectral analysis as a diagnostic tool for different Ti implant alloys to determine the percentage of components and additions that are known to cause allergies. Different materials, such as sponge Ti, TiAl6Nb7, Ti21SRx, TiAl6V4 (forged alloy), TiAl6V4 (cast alloy), TMZF, pure Ti (c. p. 1), and iodide Ti were analyzed for the presence of the elements associated with allergic reactions using spectral analysis. All of the implant material samples contained traceable amounts of Be, cadmium (Cd), Co, up to a maximum of 0.001% by weight (wt.%), Cr up to 0.033 wt.%, Cu up to 0.007 wt.%, hafnium (Hf) up to 0.035 wt.%, manganese (Mn) up to 0.007 wt.%, Ni up to 0.031 wt.%, and Pd up to 0.001 wt.%. This paper demonstrates that all the investigated implant material samples contained a low but consistent percentage of components that have been associated with allergies. Therefore, they can be virtually classified as "impurities".[57] A rat model revealed degenerative changes in osseous integration and/or in the bone around implants upon excessive occlusal loading. These results emphasize the risks associated with immediate loading and overloading. This is the first study to reveal the possibility of bone loss around overloaded implants in the absence of infection based on a small animal model.[58] Oral allergies are often underdiagnosed by dental health professionals. Patients with an oral allergy complain of various symptoms, such as burning or tingling sensations, with or without oral dryness or loss of taste, or of more general symptoms, such as headache, dyspepsia, asthenia, arthralgia, and myalgia.[59] The signs of oral allergy include erythema, labial edema (or purpuric patches on the palate), oral ulcers, gingivitis, geographical tongue, angular cheilitis, and perioral eczematous eruption (or lichenoid reactions localized on the oral mucosa). There is an increase in the prevalence of oral allergies to metals used in dental materials.[59] In order to provoke

an allergic reaction, Ti must have antigenic properties and must be in contact with the organism. The insertion of Ti implants and their permanence in the human body enhances the amount of internal exposure, and it has been proven that Ti ions concentrate in tissues surrounding dental and orthopedic implants, as well as in regional lymph nodes and pulmonary tissue.[60] Concentrations of between 100 and 300 ppm have been measured in peri-implant tissues, and are often accompanied by discolorations. An allergic reaction can be reasonably suspected after dental implant placement, on the basis of signs or symptoms associated with allergy, such as rash, urticaria, pruritus, swelling in the orofacial region, oral or facial erythema, eczematous lesions of the cheeks, or hyperplastic lesions of soft tissue (the peri-implant mucosa).[60]

6.3 | Disease symptoms

Recent reports have questioned whether metal sensitivity may occur after exposure to Ti. The emergence of facial eczema occurred in association with a Ti dental implant placed for a mandibular overdenture supported by two implants. Complete remission was achieved by the removal of the Ti material. This clinical report raises the possibility that in rare circumstances, for some patients, the use of Ti dental implants may induce an allergic reaction.[61] The incidence of Ti hypersensitivity or allergy is still unknown and the discussion on its existence is ongoing. Unexplained implant failures have also forced dental clinicians to investigate the possibility of Ti hypersensitivity or allergy.[62] Placing permanent metal dental implants in allergic patients can provoke type IV or I reactions. Several symptoms have been described, from skin rashes and implant failure, to nonspecific immune suppression. A significantly higher risk of positive allergic reaction was found in patients showing postoperative allergy compatible response group (ACRG), in which cases allergy tests could be recommended.[56] This review supports the need for long-term clinical and radiographic follow-up of all implant patients who are sensitive to metals.[54] Covani et al[63] showed that histologic analysis at the level of abutment/implant interface in two-stage implants identified heavy bacterial colonization. These findings appear to support those studies showing bacteria penetration at the level of the micro-gap, which can legitimate the hypothesis that the micro-gap at the bone level could present a risk for bone loss caused by bacterial colonization. Pigatto et al[64] reported on a case of severe systemic allergic contact dermatitis was caused by allergy to metals released by galvanic corrosion between an Hg amalgam tooth filling and an endosseous Ti dental implant. Removing the Hg-containing amalgam filling and the metal-ceramic crown on the dental Ti implant reduced considerably intraoral electrochemical corrosion process, which likely released metal ions (Hg, Cu, Ni, and Ag) into the saliva and the oral mucosa. Systemic contact dermatitis resolved completely within 8 months after the removal of both Hg amalgam tooth filling and a single metal-ceramic crown restoration (gold/Pd-based crown), which were in close proximity to each other.[64] Peri-implant diseases are a cluster of "contemporary" oral infections in humans that have emerged as a result of the routine application of osseointegrated dental implants in clinical practice. They are characterized by the inflammatory destruction of the implant-supporting tissues, as a result of biofilm formation on the implant surface.[65] The microbial composition of peri-implantitis-associated biofilms is mixed, nonspecific, and very similar to that of periodontitis. A considerable exception is the frequent presence of high numbers of staphylococci and enteric bacteria in peri-implantitis. Peri-implantitis is marked by a more extensive inflammatory infiltrate and innate immune response, a greater severity of tissue destruction, and a faster progression rate.[65] Dental peri-implantitis is characterized by a multifactorial etiology. In a prospective pilot study, Fretwurst et al[66] biopsied 12 patients (seven bone samples, five mucosal samples) who were included and analyzed. In 9 of the 12 samples (75%), the synchrotron radiation X-ray fluorescence spectroscopy (SRXRF) examination revealed the existence of Ti and an associated occurrence with Fe. Metal particles were detected in peri-implant soft confirmed with polarized light microscopy (PLM). In samples with increased Ti concentration, lymphocytes were detected, whereas M1 macrophages were predominantly seen in samples with metal particles. Ti and Fe elements were found in soft and hard tissue biopsies retrieved from peri-implantitis.[66] Studies also show the progression of periodontal disease in subjects who initially showed no traditional signs or symptoms of periodontal disease; these often have bacteria, especially those of the spirochete morphogroup, in the gingival sulci. Patients with these types of spirochetes were three times more likely to develop periodontitis within a year in the implant sites tested than those that remained healthy.[67] The pathogentic-related spirochetes are the most likely to cause infection. Based on many years of microscopic examination of bacteria-populating infections associated with failing implants, many morphologic types of spirochetes have been observed. Spirochetes seem to be a "marker bacteria" in periodontal infections that cause bone loss and implant failure.[67]

Exfoliative cheilitis is possibly caused by Hg-containing dental amalgam in close proximity to dental Ti implant. There was a strong temporal relation between last Ti dental implant and the onset of exfoliative cheilitis. "Dental implants should not be implanted in the vicinity of the Hg-containing dental amalgam filling, even in the presence of Hg amalgam as root-end filling material".[68]

Pigatto et al[68] also found in their cohort between 2001 and 2010, that the incidence of cheilitis associated with alloy-based dental restorations was 6.7% (33 of 492 patients, median age 51 years, and 75,76% were women). Patient-related risk factors for cheilitis associated with metals include mainly orthodontic appliances, dental Ti implants, and/or Hg amalgam. Acidic environments coupled with rubbing are able to introduce noticeable morphological changes and corrosion on the surface of pure Ti (cpTi) and the alloy Ti6Al4V Ti grades.[69] Ti ions may be partly responsible for the infiltration of monocytes and osteoclast differentiation by increasing the sensitivity of gingival epithelial cells to microorganisms in the oral cavity. Therefore, Ti ions may be involved in the deteriorating effects of peri-implant mucositis, which can develop into peri-implantitis accompanied by alveolar bone resorption.[70] Environmental conditions adversely affect implants' fatigue performance. This fact should

be taken into account when evaluating the mechanical properties of dental implants.[71] Data demonstrate that noxious effects are induced by high fluoride concentration, as well as low pH in the oral cavity. Therefore, such conditions should be considered when prophylactic actions are administrated in patients containing Ti implants or other dental devices.[72]

Yellow nail syndrome is characterized by nail changes, respiratory disorders, and lymphedema. Yellow nail syndrome is caused by Ti.[73] Yellow nail syndrome and Lichen planus or lichenoid reactions can originate from close or identical etiologies. They may result from dental restorative materials or metal allergy. Interestingly, the nail sometimes returns to its normal condition, months after the withdrawal of the offending agents.[74] Numerous systemic emergency situations, such as hypotension or allergic reactions, may be encountered during dental treatment. In addition, rare but life-threatening complications such as foreign body aspiration in the air passages may also be seen. Aspirated foreign bodies include teeth, implants, mechanical supports, or materials used during procedures.[75] Within limitations, a history of periodontitis is estimated to be a statistical risk factor for the long-term survival of dental implants. This negative effect would be most evident in patients with aggressive periodontitis, severe periodontitis, or after a longer follow-up.[76] Several systemic diseases (and relative medications) have been reported to impair or in some cases complicate dental implant surgery. When dealing with patients suffering from systemic diseases, the monitoring of the medical condition and of the related postoperative complications is of great importance in order to avoid risks, which could jeopardize the health of the patient.[77]

7 | CONCLUSION

This review is based on current Ti research demonstrating the many factors that can pose a negative impact on human health when exposed to the various forms of Ti, including its relationship and interactions with other metals. We looked at environmental, medical, and dental devices to show how these exposures can impact human health. Most of the literature available indicates an increased risk to allergies due to Ti exposure. These allergies are also associated with particular genetic individual factors, which validate the need for the use of precision medicine in these particular patients. We need to continue to expand our knowledge on the genetic factors associated with Ti and metal exposure in order to provide better management and care to this group of susceptible populations, which are at a higher risk. There are many available tests that can be administered prior to any medical or dental procedure that can determine allergic reactions and biocompatibility for individual patients. Most of the medical and dental practitioners commonly overlook these allergy tests increasing a health risk to the patients. These types of tests should always be utilized to allow for the most suitable materials to be used on an individual patient. Based on this review, it would be prudent to reduce the risk to all patients when considering exposure to Ti, and to avoid its improper use as much as possible. Moreover, when a patient has Ti implants it is critically important to take the utmost care to protect the patient from any and all risks of potential harm.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

1. Ti (Ti) Chemical element Written by: The Editors of Encyclopedia Britannica. [Accessed 2009] Available from http://www.britannica.com/science/Ti
2. Rollerova E, Tulinska J, Liskova A, et al. Ti dioxide NPs: some aspects of toxicity/focus on the development. Endocr Regul. 2015;49:97–112.
3. Kumazawa R, Watari F, Takashi N. Effects of Ti ions and particles on neutrophil function and morphology. Biomaterials. 2002;17:3757–64.
4. Olmedo DG, Tasat DR, Duffo G, et al. The issue of corrosion in dental implants: a review. Acta Odontol Latinoam. 2009;22:3–9.
5. Khan M, Naqvi AH, Ahmad M. Comparative study of the cytotoxic and genotoxic potentials of zinc oxide and titanium dioxide nanoparticles. Toxicol Rep. 2015;2:765–74.
6. Ghosh M, Chakraborty A, Mukherjee A. Cytotoxic, genotoxic and the hemolytic effect of Ti dioxide (TiO_2) NPs on human erythrocyte and lymphocyte cells in vitro. J Appl Toxicol. 2013;33:1097–110.
7. Dobrzyńska MM, Gajowik A, Radzikowska J, et al. Genotoxicity of silver and Ti dioxide NPs in bone marrow cells of rats in vivo. Toxicology. 2014;315:86–91.
8. Olmedo D, Tasat D, Duffó G, et al. Systemic and local tissue response to Ti corrosion. Pitting corrosion. InTech. 2012;5:93–118.
9. Ribeiro AR, Gemini-Piperni S, Travassos R, et al. Trojan-like internalization of anatase Ti dioxide NPs by human osteoblast cells. Sci Rep. 2016;6:23615.
10. Disdier C, Devoy J, Cosnefroy A, et al. Tissue biodistribution of intravenously administrated Ti dioxide NPs revealed blood-brain barrier clearance and brain inflammation in rat. Part Fibre Toxicol. 2015;12:27.
11. Yamashita K, Yoshioka Y, Higashisaka K, et al. Silica and Ti dioxide NPs cause pregnancy complications in mice. Nat Nanotechnol. 2011;5:321–8.
12. Mohammadipour A, Fazel A, Haghir H, et al. Maternal exposure to Ti dioxide NPs during pregnancy; impaired memory and decreased hippocampal cell proliferation in rat offspring. Environ Toxicol Pharmacol. 2014;2:617–25.
13. Garcia-Contreras R, Sugimoto M, Umemura N, et al. Alteration of metabolomic profiles by Ti dioxide NPs in human gingivitis model. Biomaterials. 2015;57:33–40.
14. Geraets L, Oomen AG, Krystek P, et al. Tissue distribution and elimination after oral and intravenous administration of different Ti dioxide NPs in rats. Part Fibre Toxicol. 2014;11:30.
15. Xu Y, Wei M-T, Ou-Yang HD, et al. Exposure to TiO_2 NPs increases Staphylococcus aureus infection of HeLa cells. J Nanobiotechnol. 2016;14:34.
16. Choi GS, Oak C, Chun B-K, et al. Ti dioxide exposure induces acute eosinophilic lung inflammation in rabbits. Ind Health. 2014;52:289–95.
17. Husain M, Wu D, Saber AT, et al. Intratracheally instilled Ti dioxide NPs translocate to heart and liver and activate complement cascade in the heart of C57BL/6 mice. Nanotoxicology. 2015;8:1013–22.

18. Xu J, Shi H, Ruth M, et al. Acute toxicity of intravenously administered Ti dioxide NPs in mice. PLoS One. 2013;8:e70618.
19. Liu H, Ma L, Zhao J, et al. Biochemical toxicity of nano-anatase in mice. Biol Trace Elem Res. 2009;129:170–80.
20. Grassian V, O'Shaughnessy PT, Adamcakova-Dodd A, et al. Inhalation exposure study of Ti dioxide NPs with a primary particle size of 2 to 5 nm. Environ Health Perspect. 2007;115:397–402.
21. Jonasson S, Gustafsson A, Koch B, et al. Inhalation exposure of nano-scaled Ti dioxide (TiO_2) particles alters the inflammatory responses in asthmatic mice. Inhal Toxicol. 2013;4:179–91.
22. Crouzier D, Selek L, Martz B-A, et al. Risk assessment of electromagnetic fields exposure with metallic orthopedic implants: a cadaveric study. Orthop Traumatol Surg Res. 2012;98:90–6.
23. Fujii Y. Sensation of balance dysregulation caused/aggravated by a collection of electromagnetic waves in a dental implant. Open J Antennas Propag. 2014;2:29–35.
24. 5th Paris Appeal Congress, 18th of May, 2015 Royal Academy of Medicine, Belgium – Idiopathic Environmental Intolerance: What Role for Electromagnetic Fields and Chemicals?. European Cancer and Environment Research Institute. [Accessed 2015 May 18] Available from http://www.ehs-mcs.org/fichiers/1432301961_Paris_Appeal_2015.pdf
25. Yakymenko I, Tsybulin O, Sidorik E, et al. Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn Biol Med. 2015;7:1–17.
26. Lai H. Studies on oxidative stress effect of radiofrequency radiation. 2015. [Accessed 2015 July 8] Available from http://www.stralskyddsstiftelsen.se/wp-content/uploads/2015/07/RF-free_radical_Lai_july2015.pdf
27. Friedrich RE, Todorovic M, Krüll A. Simulation of scattering effects of irradiation on surroundings using the example of Ti dental implants: a Monte Carlo approach. Anticancer Res. 2010;5:1727–30.
28. Friedrich RE, Todorovic M, Heiland M, et al. Scattering effects of irradiation on surroundings calculated for a small dental implant. Anticancer Res. 2012;5:2043–6.
29. Beyzadeoglu M, Dirican B, Oysul K, et al. Evaluation of scatter dose of dental Ti implants exposed to photon beams of different energies and irradiation angles in head and neck radiotherapy. Dentomaxillofac Radiol. 2006;35:14–7.
30. Ihde S, Kopp S, Gundlach K, et al. Effects of radiation therapy on craniofacial and dental implants: a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:56–65.
31. Harrison JS, Stratemann S, Redding SW. Dental implants for patients who have had radiation treatment for head and neck cancer. Spec Care Dentist. 2003;23:223–9.
32. Chambrone L, Mandia J Jr, Shibli JA, et al. Dental implants installed in irradiated jaws: a systematic review. J Dent Res. 2013;92(12 suppl):119S–30S.
33. Ideta T, Yamazaki M, Kudou S, et al. Investigation of radio frequency heating of dental implants made of Ti in 1.5 tesla and 3.0 tesla magnetic resonance procedure: measurement of the temperature by using tissue-equivalent phantom. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2013;69:521–8.
34. Mathew CA, Maller S, Maheshwaran. Interactions between magnetic resonance imaging and dental material. J Pharm Bioallied Sci. 2013;5(suppl 1):S113–6.
35. Madani ZS, Sefidgar SA, Rashed Mohasel A, et al. Comparative evaluation of antimicrobial activity of two root canal sealers: MTA Fillapex and AH 26. Minerva Stomatol. 2014;63:267–72.
36. Pulgar R, Segura-Egea JJ, Fernández MF, et al. The effect of AH 26 and AH plus on MCF-7 breast cancer cell proliferation in vitro. Int Endod J. 2002;35:551–6.
37. Dentsply DeTrey – AH 26 – AH 26 silverfree (Root Canal Sealer). [Accessed 1999 May 19] Available from http://www.dentsply.es/DFU/eng/DFU_AH_26_eng.pdf
38. MTA Fillapex Technical Profile (Root Canal Sealer). [Accessed 2016 March] Available from http://www.angelusdental.com/img/arquivos/mta_fillapex_technical_profile_download.pdf
39. Huang FM, Tai KW, Chou MY, et al. Cytotoxicity of resin-, zinc oxide-eugenol and calcium hydroxide-based root canal sealers on human periodontal ligament cells and permanent V79 cells. Int Endod J. 2002;35:153–8.
40. Konjhodzic-Prcic A, Gorduysus O, Kucukkaya S, et al. In vitro comparison of cytotoxicity of four root canal sealers on human gingival fibroblasts. Med Arch. 2015;69:24–7.
41. Reszka P, Nowicka A, Lipski M, et al. A comparative chemical study of calcium silicate-containing and epoxy resin-based root canal sealers. Biomed Res Int. 2016;2016:9808432.
42. Frydman A, Simonian K. Review of models for Ti as a foreign body. J Calif Dent Assoc. 2014;42:829–33.
43. Fage SW, Muris J, Jakobsen S, et al. Titanium: a review on exposure, release, penetration, allergy, epidemiology, and clinical reactivity. Contact Dermatitis. 2016;74:323–45.
44. Chaturvedi T. Allergy related to dental implant and its clinical significance. Clin Cosmet Investig Dent. 2013;19:57–61.
45. Gittens RA, Olivares-Navarrete R, Tannenbaum R, et al. Electrical implications of corrosion for osseointegration of Ti implants. J Dent Res. 2011;90:1389–97.
46. Lee J-J, Song K-Y, Ahn S-G, et al. Evaluation of effect of galvanic corrosion between nickel-chromium metal and Ti on ion release and cell toxicity. J Adv Prosthodont. 2015;7:172–7.
47. Zohdi H, Emami M, Shahverdi HR. Galvanic Corrosion Behavior of Dental Alloys. 2012;157–68. https://doi.org/10.5772/52319
48. Bhola R, Bhola SM, Mishra B, et al. Corrosion in Ti dental implants/prostheses – a review. Trends Biomater Artif Organs. 2011;25:34–46.
49. Javed F, Al-Hezaimi K, Almas K, et al. Is titanium sensitivity associated with allergic reactions in patients with dental implants? A systematic review. Clin Implant Dent Relat Res. 2013;15:47–52.
50. Thomas P, Braathen LR, Dorig M, et al. Increased metal allergy in patients with failed metal-on-hip arthroplasty and peri-implant T-lymphocytic inflammation. Allergy. 2009;64:1157–65.
51. Vijayaraghavan V, Sabane AV, Tejas K. Hypersensitivity to Ti: a less explored area of research. J Indian Prosthodont Soc. 2012;12:201–7.
52. Müller K, Valentine-Thon E. Hypersensitivity to Ti: clinical and laboratory evidence. Neuro Endocrinol Lett. 2006;27(suppl 1):31–5.
53. Sodor A, Ogodescu AS, Petreuş T, et al. Assessment of orthodontic biomaterials' cytotoxicity: an in vitro study on cell culture. Rom J Morphol Embryol. 2015;56:1119–25.
54. Siddiqi A, Payne AG, De Silva RK, et al. Ti allergy: could it affect dental implant integration? Clin Oral Implants Res. 2011;22:673–80.
55. Syed M, Chopra R, Sachdev V. Allergic reactions to dental materials-a systematic review. J Clin Diagn Res. 2015;9:ZE04–9.
56. Sicilia A, Cuesta S, Coma G, et al. Ti allergy in dental implant patients: a clinical study on 1500 consecutive patients. Clin Oral Implants Res. 2008;19:823–35.
57. Harloff T, Hönle W, Holzwarth U, et al. Ti allergy or not? "Impurity" of Ti implant materials. Health. 2010;2:306–10.
58. Nagasawa M, Takano R, Maeda T, et al. Observation of the bone surrounding an overloaded implant in a novel rat model. Int J Oral Maxillofac Implants. 2013;28:109–16.
59. Evrard L, Waroquier D, Parent D. Allergies to dental metals. Ti: a new allergen. Rev Med Brux. 2010;31:44–9.
60. Goutam M, Giriyapura C, Mishra SK, et al. Ti allergy: a literature review. Indian J Dermatol. 2014;59:630.
61. Egusa H, Ko N, Shimazu T, et al. Suspected association of an allergic reaction with Ti dental implants: a clinical report. J Prosthet Dent. 2008;100:344–7.

62. Bilhan H, Bural C, Geckili O. Ti hypersensitivity. A hidden threat for dental implant patients? N Y State Dent J. 2013;79:38–43.
63. Covani U, Marconcini S, Crespi R, et al. Bacterial plaque colonization around dental implant surfaces. Implant Dent. 2006;15:298–304.
64. Pigatto PD, Brambilla L, Ferrucci S, et al. Case presentation: systemic allergic contact dermatitis associated with allergy to intraoral metals. Dermatol Online J. 2014;20.
65. Belibasakis GN. Microbiological and immuno-pathological aspects of peri-implant diseases. Arch Oral Biol. 2014;59:66–72.
66. Fretwurst T, Buzanich G, Nahles S, et al. Metal elements in tissue with dental peri-implantitis: a pilot study. Clin Oral Implants Res. 2016;9:1178–86.
67. Nordquist W. Oral spirochetosis associated with dental implants: important clues to systemic disease. Int J Clin Implant Dent. 2009;1:32–9.
68. Pigatto PD, Berti E, Spadari F, et al. Photoletter to the editor: Exfoliative cheilitis associated with Ti dental implants and Hg amalgam. J Dermatol Case Rep. 2011;5:89–90.
69. Wheelis SE, Gindri IM, Valderrama P, et al. Effects of decontamination solutions on the surface of Ti: investigation of surface morphology, composition, and roughness. Clin Oral Implants Res. 2016;27:329–40.
70. Wachi T, Shuto T, Shinohara Y, et al. Release of Ti ions from an implant surface and their effect on cytokine production related to alveolar bone resorption. Toxicology. 2015;327:1–9.
71. Shemtov-Yona K, Rittel D, Levin L, et al. The effect of oral-like environment on dental implants' fatigue performance. Clin Oral Implants Res. 2014;25:e166–70.
72. Noguti J, de Oliveira F, Peres RC, et al. The role of fluoride on the process of Ti corrosion in oral cavity. Biometals. 2012;25:859–62.
73. Berglund F, Carlmark B. Ti, sinusitis, and the yellow nail syndrome. Biol Trace Elem Res. 2011;143:1–7.
74. Baran LR. Yellow nail syndrome and nail lichen planus may be induced by a common culprit. Focus on dental restorative substances. Front Med (Lausanne). 2014;1:46.
75. Eroglu O, Algan-Kaya H, Coskun F. A potentially fatal complication that may occur during dental treatment: "foreign body aspiration". Pan Afr Med J. 2015;20:36.
76. Wen X, Liu R, Li G, et al. History of periodontitis as a risk factor for long-term survival of dental implants: a meta-analysis. Int J Oral Maxillofac Implants. 2014;29:1271–80.
77. Donos N, Calciolar E. Dental implants in patients affected by systemic diseases. Br Dent J. 2014;217:425–30.

How to cite this article: Tibau AV, Grube BD, Velez BJ, Vega VM, Mutter J. Titanium exposure and human health. *Oral Sci Int*. 2019;16:15–24. https://doi.org/10.1002/osi2.1001